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| EXAMINER | |
|---|---|
| HUYNH, PHUONG N | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/728,051 | CAPLAN, MICHAEL J. | |
| | Examiner | Art Unit | |
| | PHUONG HUYNH | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10/16/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *34-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 34-45 are pending are being acted upon in this Office Action.

2. In view of the amendment filed October 16, 2008, the following rejections remain.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 34-43 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,097,141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892).

The WO 99/38978 publication teaches production of recombinant modified allergen such as modified peanut allergen Ara h1 (Table 4), modified peanut allergen Ara h2 (Table 2) and modified peanut allergen (Table 6), see reference page 10, lines 10-16, Table 4-6, in particular. The recombinant modified allergen is expressed in host cell such as bacteria *E coli* strain BL21 (DE3), see page 10, line 13, page 16, line 29, in particular. The WO 99/38978 publication teaches a pharmaceutical composition comprising *E coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2 and Ara h3 where the center of one or more amino acid present in IgE binding sites of Ara h1, Ara h2 and Ara h3 have been substituted with neutral or hydrophilic amino acid or lacks a portion of the wild-type peanut allergen such that the modified peanut allergens have reduced binding to IgE as compared to the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, claims 1-7 of the WO 99/38978 publication, in particular). The reference wild-type Ara h3 allergen of SEQ ID NO: 6 is encoded by the reference nucleotide sequence of SEQ ID NO: 5, which is identical to the claimed

SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular). The reference IgE binding sites of Ara h1, Ara h2 and Ara h3 are shown in Table 4 at page 23, Table 5 at page 24 and Table 6 at page 24, respectively. The reference wild-type Ara h1 of SEQ ID NO: 2 is encoded by the reference SEQ ID NO: 1. The reference wild-type Ara h2 of SEQ ID NO: 4 is encoded by the reference SEQ ID NO: 3. The reference further teaches a method of making modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the modified peanut allergen or portion thereof has at least one amino acid that has been deleted or substituted within the IgE binding sites such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, claims 29-in particular). The reference modified peanut allergen is encapsulated inside the dead *E coli* because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm since it must be solubilized with urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular). The reference's modified peanut allergens Ara h1, Ara h2 and Ara h3 are identical to the ones to be incorporated by reference to 09/141,220. The WO 99/38978 publication teaches the modified peanut allergen is safe and efficacious for treating peanut allergy (see page 2, lines 21, claim 36 of the publication, in particular). The advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular).

The claimed invention differs from the teachings of the reference only in that the pharmaceutical composition wherein the modified peanut allergen is encapsulated in *E coli* and the *E coli* is dead instead of alive and the *E coli* was killed by heat.

Fenton et al teach a pharmaceutical composition comprising dead *Escherichia coli* that have been engineered to express recombinant modified ras protein bearing a Gln to Leu mutation at residue 61 and a pharmaceutical carrier such as Hanks Balance Salt solution or HBSS (see page 1855, col. 1, Immunization with heat-killed bacteria, in particular). The reference *E coli* were heat-killed by incubation at 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). The reference recombinant Ras protein obviously located in side the *E coli* such as

inclusion bodies located within the cytoplasm given the purification of Ras protein must be disrupted with sonification (see page 1854, col. 2, Purification of Ras proteins, in particular). Fenton et al further teach antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the recombinant modified protein derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity by modulating immune response to Th1 as measured by cytokines IL-2, IFNγ secreted and granuloma formation at the vaccine site (see page 1857, col. 2, full paragraph, page 1860, col. 2, second full paragraph, in particular).

Vrtala et al teach the use of recombinant non-pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy of type I allergy in patients (see page 293, col. 2, in particular).

The '799 patent teaches the use of *E coli* as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular). The '799 patent teaches the antigen or allergen of interest in the *E coli* can be engineered to transport across the *E coli* cytoplasmic membrane end ended up in the periplasmic space (see col. 14, line 29-31, in particular). The bacterial cell is formulated for administered orally in enteric-coated capsules (see col. 13, line 4-6, in particular).

The '141 patent teaches a method of modifying anaphylactogens which reduces toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* by heating *E coli* from about 50 to 100 °C to reduce toxicity of the antigens (see col. 1, lines 8-65, col. 2, line 1-10, in particular). The '141 patent further teaches *E coli* can be killed by chemical treatment such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide $H_2O_2$ (see col. 1, line 58, in particular).

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed bacteria by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the *E coli* that is expressed the modified peanut allergen Ara h1, Ara h2 and Ara h3 with reduced ability to bind to or cross-link IgE of the WO 99/38978 publication as an allergen carrier for induction of tolerance as taught by the '799 patent by killing the *E coli* bacteria by heating from about 50 to 100°C as taught by Fenton or the '141 patent or Lecberc et al or oxidizing agent such as Hydrogen peroxide as taught by the '141 patent to avoid any ethical issues and without the need for extensive protein purification using such bacteria for treating allergy as taught by Vrtala et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify allergen because the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to kill the *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the technical and ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al further teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification while avoiding the ethical problems of such *live* allergy vaccines (see page 293, col. 2, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to use heat killed recombinant bacteria expressing the antigen of interest because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine carrier and that the antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific

immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1857, col. 2, full paragraph, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular). The '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Applicants' arguments filed October 16, 2008 and February 29, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the '978 publication, whether alone or in combination with any of the cited references, does not teach or suggest a modified allergen "encapsulated inside" dead *E. coli*, as recited in the present claims. Furthermore, the '978 publication does not teach or suggest any pharmaceutical composition comprising encapsulated peanut allergens, as recited in the present claims. Indeed, as has been extensively discussed, several of the secondary references teach explicitly away from the claimed invention. To give but one example, some secondary references require live bacteria. There is absolutely no combination of these cited references that could teach or suggest the claimed invention.

The sole statement made by the Examiner with regard to "encapsulated inside" is that urea is used to solubilize a protein produced in the '978 publication. This statement is wholly irrelevant to the present claims.

First, the protein being solubilized with urea in the '978 publication is not a modified peanut allergen as recited in the present claims. That is, the '978 publication is describing urea purification of a different protein.

Second, the fact that the '978 inventors used urea in purifying a protein does not mean that the protein is "encapsulated within" bacteria.

Third, clearly, if the '978 inventors are isolating protein from dead E. coli, they are not preparing the dead E. coli as a pharmaceutical composition, as recited in the present claims.

For all of these reasons, the '978 publication cannot teach or suggest pharmaceutical compositions of modified allergens encapsulated inside dead E. coli. The Examiner cannot continue to ignore these points.

No list of secondary references, however long, is meaningful unless the cited secondary references in fact address the deficiencies of the primary reference. Moreover, the Examiner must take the teachings of the secondary references as a whole and may not ignore those portions that inconveniently teach away from the Examiner's intended combination, or from the claimed invention.

The "new" rejections levied in the Office Action add nothing substantive to the previously-levied rejections, yet the Office Action has not a single remark addressing, or even acknowledging, Applicant's prior arguments or amendments made in the Response submitted on February 29, 2008.

In response to the argument that the '978 publication does not teach or suggested a modified allergen "encapsulated inside" dead *E coli*, as recited in the present claims, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Contrary to applicants' assertion that the WO/38978 publication does not teach modified allergen, in addition to expressing wild type allergen (i.e., Ara h2), the WO/38978 publication teaches production of recombinant modified allergen such as modified peanut allergen Ara h1 (Table 4), modified peanut allergen Ara h2 (Table 2) and modified peanut allergen (Table 6), see reference page 10, lines 10-16, Table 4-6, in particular. The recombinant modified allergen is expressed in host cell such as bacteria *E coli* strain BL21 (DE3), see page 10, line 13, page 16, line 29, in particular. In fact, the instant specification at page 44 discloses the use of the same bacteria *E coli* strain BL21 (DE3) as disclosed by the WO/38978 publication. Further, page 27 of instant specification discloses production of recombinant or modified allergen, See page 27, lines 4-8. The reference recombinant modified allergen in the *E coli* is not secreted (encapsulated inside the *E coli*) because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm and must be lysis in denaturing binding buffer such as urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular).

The claimed invention differs from the teachings of the reference only in that the pharmaceutical composition wherein the modified peanut allergen is encapsulated in *E coli* and the *E coli* is dead instead of alive and the *E coli* was killed by heat.

Fenton et al teach a pharmaceutical composition comprising dead *Escherichia coli* that have been engineered to express recombinant modified ras protein bearing a Gln to Leu mutation at residue 61 and a pharmaceutical carrier such as Hanks Balance Salt solution or HBSS (see page 1855, col. 1, Immunization with heat-killed bacteria, in particular). The reference *E coli* were heat-killed by incubation at 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). The reference recombinant Ras protein obviously located in side the *E coli* such as inclusion bodies located within the cytoplasm given the purification of Ras protein must be disrupted with sonification (see page 1854, col. 2, Purification of Ras proteins, in particular). Fenton et al further teach antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the recombinant modified protein derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity by modulating immune response to Th1 as measured by cytokines IL-2, IFNγ secreted and granuloma formation at the vaccine site (see page 1857, col. 2, full paragraph, page 1860, col. 2, second full paragraph, in particular).

Vrtala et al teach the use of recombinant non-pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy of type I allergy in patients (see page 293, col. 2, in particular).

The ‘799 patent teaches the use of *E coli* as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular). The ‘799 patent teaches the antigen or allergen of interest in the *E coli* can be engineered to transport across the *E coli* cytoplasmic membrane end

ended up in the periplasmic space (see col. 14, line 29-31, in particular). The bacterial cell is formulated for administered orally in enteric-coated capsules (see col. 13, line 4-6, in particular).

The '141 patent teaches a method of modifying anaphylactogens which reduces toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* by heating *E coli* from about 50 to 100 °C to reduce toxicity of the antigens (see col. 1, lines 8-65, col. 2, line 1-10, in particular). The '141 patent further teaches *E coli* can be killed by chemical treatment such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide $H_2O_2$ (see col. 1, line 58, in particular).

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed bacteria by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the *E coli* that is expressed the modified peanut allergen Ara h1, Ara h2 and Ara h3 with reduced ability to bind to or cross-link IgE of the WO 99/38978 publication as an allergen carrier for induction of tolerance as taught by the '799 patent by killing the *E coli* bacteria by heating from about 50 to 100°C as taught by Fenton or the '141 patent or Lecberc et al or oxidizing agent such as Hydrogen peroxide as taught by the '141 patent to avoid any ethical issues and without the need for extensive protein purification using such bacteria for treating allergy as taught by Vrtala et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify allergen because the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to kill the *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the technical and ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in

patients (see page 293, col. 2, in particular). Vrtala et al further teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification while avoiding the ethical problems of such *live* allergy vaccines (see page 293, col. 2, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to use heat killed recombinant bacteria expressing the antigen of interest because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine and that the antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFNγ secreted (see page 1857, col. 2, full paragraph, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular). The '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

With respect to the argument that the '978 publication used urea in purifying a protein does not mean that the protein is "encapsulated within" bacteria, at the very least, the protein is not secreted since the protein is produced as inclusion bodies. Since the protein is not secreted, then the protein must be encapsulated. Even assuming the '978 publication does not teach encapsulated protein as argued, Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest in the periplasm (which meets the definition of encapsulated within the bacteria) instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). The '799 patent teaches allergen encapsulated in the *E coli* such as cytoplasmic and/or periplasmic allergen released by the carrier upon death of the bacteria (see col. 9, lines 3-40, in particular). Finally, it is noted that the specification discloses the dead E coli expressing the modified peanut allergens is encapsulated in PLGA, chitosan, lipsomes or hydrogel, not allergen encapsulated in bacteria as claimed, see page 34.

With respect to the argument that the '978 publication does not teach or suggest any pharmaceutical composition, it is noted that Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest wherein the antigen is encapsulated in the periplasm instead of secreted and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). The '799 patent teaches pharmaceutical composition comprising *E coli* bacteria expressing antigen or allergen as a carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable since upon the death of the micro, the antigen/allergen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular).

With respect to the argument that secondary reference teach explicitly away from the claimed invention such as require *live* bacteria instead of dead bacteria, Leclerc et al teach a pharmaceutical composition comprising heat-killed or dead recombinant *E coli* expressing any antigen of interest wherein the antigen is encapsulated in the periplasm instead of secreted and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Further, the recitation of "dead" *E coli* is an obvious variation of the teachings of the reference '799 patent since the '799 patent teaches live as well as dead *E coli;* the *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the bacteria carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular).

With respect to the argument that the '978 publication describes expression of a wild type allergen (i.e., Ara h2) and not modified allergen, the '978 publication exemplified recombinant expression of wild type allergen i.e., Ara h2, see page 16. In addition, the WO/38978 publication teach recombinant production of modified allergen, see page 10. The WO/38978 publication teaches production of recombinant modified allergen such as modified peanut allergen Ara h1 (Table 4), modified peanut allergen Ara h2 (Table 2) and modified peanut allergen (Table 6), see reference page 10, lines 10-16, Table 4-6, in particular. The recombinant production is expressed in host cell including bacteria, see page 10, lines 10-13, in particular.

With respect to the argument that the Fenton et al teach a pharmaceutical composition comprising dead *E. coli* that express a particular modified Ras protein and not modified allergen that will be used to immunize a subject and teaches away from immunization using cells comprising modified allergens, Fenton teach the use of dead *E coli* expressing an antigen of interest and the dead *E coli* is used carrier for a pharmaceutical composition. Likewise, the '799 patent teaches the use of dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). Although Fenton et al and the '799 patent do not teach the modified peanut allergen, the '978 publication teaches modified peanut allergens and expressed in *E coli* discussed supra.

A prior art reference from a different field may serve as analogous art if it is reasonably pertinent to the problem addressed by the application, see *In re Icon Health & Fitness*, Inc. No. 06-1573 (Fed. Cir. Aug. 1, 2007). In this case, the use as dead *E coli* as antigen carrier for vaccine or pharmaceutical composition is well known in the field of vaccine immunology at the time of the invention may have led one skilled in the art to look into Leclerc et al who teach encapsulated heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm as a vaccine carrier (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Likewise, Fenton et al teach the use of dead *E coli* expressing recombinant antigen of interest as a carrier for a pharmaceutical composition. The '799 patent also teaches the use of live or dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular). The *E coli* as carrier can be killed by heat or chemical as taught by the '141 patent. The expected advantage of using bacteria expressing modified allergen as allergy vaccine is that it does not have the need for extensive protein purification using bacteria transformed with any cDNA encoding the modified allergen of interest as taught by Vrtala et (see page 293, col. 2, in particular).

Contrary to applicants' assertion that there is no motivation for one of ordinary skill to modify the teachings of the '978 publication to achieve encapsulation of (1) modified allergen; in (2) dead *E coli* that were (3) killed by heat, the strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been

produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

In this case, one having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen because peanut is highly anaphylactic and the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed bacteria *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed *E coli* bacteria as vaccine carrier because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine since antigen presenting cell such as macrophage can phagocytose the bacteria *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFN$\gamma$ secreted (see page 1857, col. 2, full paragraph, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use heat-killed *E coli* bacteria because Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use bacteria *E coli* as a vaccine carrier because the '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for

treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to kill bacteria with heat because the '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since recombinant production of modified peanut allergen in *E coli* is known at the time of the invention and combining the prior art elements of using dead *E coli* (killed by heat or chemical) expressing modified allergen in periplasm (encapsulated) or cytoplasm as a carrier for induction of tolerance is desirable and have been predictable at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention. An obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See

*KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007).* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

With respect to the argument that Vrtala et al teach feeding of recombinant attenuated Salmonella that express modified birch pollen allergens to mice and does not teach dead *E coli*, as stated above, Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest. Likewise, the '799 patent teaches also the use of dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). Vrtala et al is merely cited for the advantage of using bacteria transformed with any cDNA coding for the modified allergen as a vaccine carrier without having the need for extensive protein purification (see page 293, col. 2, in particular). As applicants pointed out, Vrtala et al teach the ethical problems associated live allergy vaccine, Vrtala et al offers one solution of using attenuated bacteria to express modified allergen. Although Vrtala et al does not teach dead *E coli*, Leclerc et al teach heat-killed recombinant *E coli* expressing any antigen of interest. The '799 patent teaches also the use of dead *E coli* bacteria as an allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular).

Contrary to applicants' assertion that the secondary references teach away the claimed invention, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

5. Claims 44-45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,0997, 141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892) as applied to claims 34-43 mentioned above and further in view of WO 92/14487 (newly cited, published

September 1992; PTO 892) and US Pat No 6,270,723 (of record, filed Oct 2, 1998; PTO 892), Komanapalli et al (newly cited, Appl Microbil Biotechnol 49: 766-769, 1998; PTO 892) and/or Ingram et al (newly cited, J Bacteriology 144(2): 481-488, Nov 1980; PTO 892).

The combined teachings of the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and Leclerc et al have been discussed supra.

The claimed invention in claim 44 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed by chemical treatment instead of heat.

The claimed invention in claim 45 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed using a chemical selected from the group consisting of bleach, ozone, and alcohols instead of heat.

The WO 92/14487 publication teaches a method of safely killing *E coli* bacteria expressing various colonization factor antigens by chemical treatment such as mild or diluted formalin-treated *E coli* for use as a whole cell vaccine (see page7-8, page 19, line 26, in particular). The WO 92/14487 publication teaches the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page 8, lines 7-9, in particular).

The '723 patent teaches various methods of killing *bacteria* by chemical treatment such as alcohol (see col. 1, line 21, in particular), bleach (see col. 10, line 39-40, in particular) or pressure sterilization (ozone) to inactivate bacteria such as *E coli* for pharmaceutical composition (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* while oxygen gas has no effect (see page 767, col. 2, results, Fig. 1, in particular). Ozone induced lipid oxidation in *E coli* and leakage of cytoplasmic contents (see abstract, see Figs 5 & 6, in particular).

Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Ingram et al teach increasing concentrations of alcohol such as ethanol and hexanol progressively inhibits the growth of *E coli* and hexanol was a much more potent inhibitor of

growth than was ethanol (see page 482, col. 2, in particular). Ingram et al teach ethanol prevented the assembly of cross-linked peptidoglycan while hexanol did not inhibit such cross-linking, see page 485, col. 2, in particular.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to kill any recombinant modified peanut allergen producing *E. coli* for a pharmaceutical composition given the highly anaphylactic nature of the peanut allergen as taught by the WO 99/38978 publication by means chemical treatment such as mild or diluted formalin-treatment as taught by the WO 92/14487 publication or diluted alcohol (see col. 1, line 21, in particular), or diluted bleach (see col. 10, line 39-40, in particular) as taught by the '723 patent or alcohol as taught by Ingram or by ozone as taught by Komanapalli et al to preserve the immunogenic property of inactivated bacteria as taught by the WO 92/14487 publication.

One having ordinary skill in the art would have been motivated to do this because the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria while at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as maintaining greater stability of the antigen against degradation in the intestinal milieu as taught by the WO 92/14487 publication (see page 8, lines 7-9, in particular). The '723 patent teaches chemical treatment such as iodine, bleach, ozone, or alcohol can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular). Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* (see page 767, col. 2, results, Fig. 1, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed October 16, 2008 and February 29, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the deficiencies of '978 publication in view of secondary references Fenton et al. and Vrtala et al exist no matter whether the E. coli are killed by heat treatment or by chemical treatment.

The arguments with respect to the deficiency of WO 99/38978 publication have been discussed supra and are incorporated here by reference.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 34-45 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-36 and 38-49 of copending Application No. 10/728,323. Although the conflicting claims are not identical, they are not patentably distinct from each other because the *species* of pharmaceutical composition comprising dead *E coli* comprising at least one modified peanut allergen amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: l, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside such as cytoplasm or periplasm of the dead *E. coli*; and a pharmaceutically acceptable carrier, as well as modified peanut allergen is located in the cytoplasm, or periplasm of dead *E coli*, and means and mode of killing by heat,

chemical treatment such as iodine, bleach, ozone or alcohol of instant application anticipates the *genus* of composition comprising at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, wherein the wild-type allergen is found in nature in foods, in peanuts, milk, eggs, seafood, nuts, dairy products, fruit, as well as modified peanut allergen is located in the cytoplasm or periplasm of the dead E coli, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of copending application 10/728,323.

Thus the issuance of a patent to instant application (species) anticipates the claims of the copending application (genus). The issuance of a patent to copending application 10/728,323 would include the claims of instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' arguments filed October 16, 2008 and February 29, 2008 have been fully considered but are not found persuasive.

It is noted that applicant defers further comment on this rejection until the claims of either application have been found to be patentable.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
January 16, 2009